THE EFFECT OF HYPOXIA ON THE REACTION TO SEVERAL PHARMACOLOGICAL COMPOUNDS.

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ABSTRACT: In experiments on white mice we studied the influence of breathing a hypoxic gas mixture (7.5 - 9.0% O_2) for a period of 1 - 4 hours on the reaction to ether, intranarcon and corasole. We established that the effect of hypoxia is associated with phase changes in the sensitivity of the animals to pharmacological compounds; the narcotic effect of ether and intranarcon is increased and the sensitivity to toxic doses of corasole is decreased. We make the conclusion that change in the reaction to the compounds under the influence of hypoxia indicates functional changes in the central nervous system with preferential development of the process of inhibition.

The problem of oxygen starvation of the organism belongs among /230 the number of very real problems in the field of physiology. Numerous studies have shown that hypoxia is accompanied by distinct changes in the functional state of different systems of the organism; its reaction to several infectious agents and other pathogenic factors is changed [1,2,14,15]. N. M. Dmitriyeva [8,9] observed a change in the reaction of the organism to cardiac glucosides with experimental hypoxia. In this respect it is of undoubted theoretical and practical interest to investigate the characteristics of the pharmacodynamics of various medicinal compounds under conditions of oxygen starvation.

In the present paper we have studied the influence of hypoxia of different durations on the reaction to several narcotics (ether, intranarcon) and analeptics (corasole).

The experiments were carried out on 480 white male mice weighing 22 - 25 g. The animals were subjected for a period of 1 - 4 hours to the effect of a hypoxic gas mixture containing 7.5 - 9.0% oxygen (the carbon dioxide content did not exceed 1 - 1.5%) in a chamber with a volume of 50 liters. The composition of the gas atmosphere was controlled with an oxygen tester and a capnograph from the firm "Godart".

Five control and five experimental animals were simultaneously given an ether narcotic in a hermetically sealed exsiccator with a volume of 9.1 liters for a period of 15 minutes with a vapor concentration of 300 mg/liter. Intranarcon in a dose of 130 - 150 mg/kg

and corasole (80 - 90 mg/kg) were injected intraperitoneally in 0.1 ml solution per 10 g of animal weight.

The sign of the reaction to intranarcon was the total time of narcosis in stages III-IV following Schoen [18,19], and in the experiments with ether, the duration of the period of awakening after cessation of narcotization. We judged the reaction of corasole from the death rate of the animals. The experimental data were analyzed statistically [13].

Immediately after placing the animals into the hypoxia atmosphere we observed in them a distinct increase in frequency and deepening of respiration, the color of the eyes took on a bluish tint, clear signs of motive stimulation were noted. After 30 - 40 minutes the animals quieted down and then no further substantial differences were noted in their behavior as compared with the control animals. The dyspnea and bluish coloration of the eyes were retained for the entire period of residence in the chamber. Study of the sensitivity to pharmacological compounds for the different periods of time of the effect of the hypoxic gas mixture permitted distinct changes to be shown in the reaction of the animals. Generalized data on the influence of hypoxia on the reaction to intranarcon are shown on Table 1. /231

TABLE 1. INFLUENCE OF HYPOXIA ON THE DURATION OF INTRANARCON NARCOSIS IN WHITE MICE.

Time of Residence in Hypoxic Atmosphere, hours	Dose of Compound mg/km	Statistical Sign	Control	Experiment
1	150,0	$M \pm m$	113,6±14,3	150,3±14,42
		% of Control	—	132,3
2	130,0	$M \pm m$	24,8±4,42	35,4±6,34
		% of Control	—	143,0
3	130,0	$M \pm m$	30,8±8,15	42,6±8,37
		% of Control	—	138,5
4	150,0	$M \pm m$	76,6±9,84	79,2±14,6
		% of Control	—	103,0

From the data given in the table it is clear that after different periods of residence of the white mice in a hypoxic gas atmosphere we noted an increase in their sensitivity with respect to the intranarcon. The most pronounced changes in the reaction were observed after 1 hour of breathing the hypoxic gas mixture (t^1 = 1.8); in the later periods (after 2 and 3 hours) the differences between the experimental and the control groups gradually decreased (t = 1.37 - 1.0) and after 4 hours practically disappeared (t = 0.15).

Taking into account the data known from the literature on the dependence of the pharmacodynamic effect of the compound on the functional state of the organism, and especially on the functional state of the physiological system which is primarily affected by the medicinal compound [11] we may assume that under the influence of breathing a hypoxic gas mixture the functional cortico-subcortical interrelationships in the central nervous system are changed. /232 Here apparently at the beginning of adaptation of the mice to hypoxia the functional tonus of the subcortical formations is characterized by a slight prevalence of the inhibition processes.

TABLE 2. INFLUENCE OF HYPOXIA ON THE DURATION OF THE INVERSE DEVELOPMENT OF ETHER NARCOSIS IN WHITE MICE.

Time of Residence in Hypoxic Atomsphere, hours	Statistical Sign	Control	Experiment
1	$M \pm m$ %	3,4±0,32 —	6,12±0,35 180,0
2	$M \pm m$ %	4,58±0,67 —	4,53±0,60 99,0
3	$M \pm m$ %	5,25±0,51 —	5,0±0,55 95,2
4	$M \pm m$ %	4,85±0,42 —	5,29±0,4 109,0

From the data given in Table 2 it is clear that breathing a hypoxic gas mixture produces in the white mice, after 1 hour, more

[1] The degree of reliability of differences between the control and the experimental animals.

pronounced changes in the sensitivity to ether than to intranarcon. In fact the duration of the inverse development of ether narcosis in these animals was substantially increased (t = 5.78). In subsequent times (2, 3 and 4 hours) no pronounced deviations were observed in the reaction to the compound being tested (see the figure).

If we assume that ether in average doses is a typical cortical narcotic [10], then we may assume that the process of inhibition at the beginning of the effect of the hypoxic mixture primarily involved the cortical structures of the brain. Along with this, the experimental results may also show a more rapid recovery of the cortical tonus of the major hemispheres. These assumptions fully agree with the literature data which indicate a greater vulnerability and a greater plasticity of the brain in comparison with the subcortical structures. Thus, the data on the reaction of the organism to narcotic compounds show that even from the first hour of adaptation to hypoxia in the cortex and the subcortical formations the processes of inhibition prevail. The increased motive activity of the animals during the first 30 - 40 minutes of breathing the hypoxic gas mixture indicates apparently the appearance of the first phase in the changes in the functional state of the central parts of the nervous system, i.e., the phase of stimulation.

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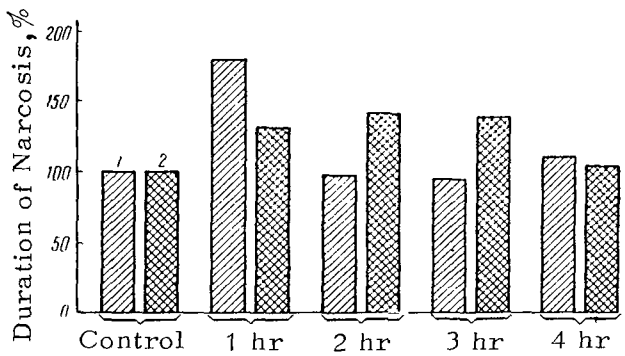

Influence of Hypoxia on the Duration of Ether (1) and Intranarcon (2) Narcosis.

TABLE 3. INFLUENCE OF HYPOXIA ON THE REACTION OF WHITE MICE TO CORASOLE.

Time of Residence in Hypoxic Atmosphere, hours	Dose of Compound mg/km	Control $P \pm m$	Experiment $P \pm m$
1	80.0—90.0	45±7.96	42±7.97
2	80.0—90.0	22.5±6.69	17.5±6.1
3	80.0—90.0	42.5±7.92	30.0±7.34
4	80.0—90.0	32.5±7.5	30.0±7.34

P ± m is the % of death rate with mean error. In each group of animals 20 of the mice received corasole in a dose of 80.0 mg/kg, and the other 20 animals received 90.0 mg/kg.

The data given on the changes in the functional state of the central nervous system under the influence of hypoxia was confirmed in the investigations with corasole (Table 3). In fact the death rate of the experimental animals in all the experiments was found /234 to be somewhat lower than in the control animals. Here the most pronounced differences were after 3 hours of breathing the hypoxic mixture (t = 1.16).

As we know, corasole exerts a stimulating effect primarily on the subcortical formations of the brain [4,5,11], being in large doses a convulsive poison. There are also indications that its effect is propagated diffusely both to the stem part of the brain and to its subcortical structures and to the cortical formations of the major hemispheres [16 - 18]. Therefore the decrease in the toxic effect of the compound in the experimental mice obviously is due to the development of inhibition processes in the central nervous system under the influence of oxygen starvation.

The effect of different pharmacological compounds, and especially narcotics, for the period of oxygen starvation has been studied by many authors [3,6,7,12], however necessary attention has not been given to the characteristics of the pharmacodynamics of the compounds being tested in the state of hypoxia.

The results of the experiments which we carried out indicate that the process of "acute acclimatization" to hypoxia is accompanied by pronounced deviations in the reaction of the organism to several pharmacological compounds.

CONCLUSIONS

1. Residence of white mice under hypoxic conditions (7.5 - 9.0% O_2) with a duration up to four hours is accompanied by phase changes in their reaction to ether, intranarcon and corasole.

2. Under the influence of hypoxia the narcotic effect of ether and intranarcon is increased, and the sensitivity to toxic doses of corasole is decreased.

3. Change under the influence of oxygen starvation in the reaction of the organism to pharmacological compounds indicates a development in the central nervous system of the process of inhibition.

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